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10/823,690	04/14/2004	Steven J. Soldin	31603-2055	5374

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EXAMINER

MUI, CHRISTINE T

ART UNIT	PAPER NUMBER
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1709

MAIL DATE	DELIVERY MODE
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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/823,690

Applicant(s)

SOLDIN, STEVEN J.

Examiner

Christine T. Mui

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-63 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-63 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 14 April 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 29 June 2006.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION

1. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

2. The abstract of the disclosure is objected to because of the inclusion of the phrase of "comprising". Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite since the preamble of the claim recites "a sample possibly containing one or more thyroid hormones," that indicates the sample may not contain any thyroid hormones therein. Part (a) of claim 1 positively claims "a sample" of a thyroid hormone. Therefore, the preamble and part (a) of claim 1 are not

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commensurate in scope with one another. The same problem can be seen in claims 28, 58 and 60.

5. Claim 12 recites the limitation "column" in line 4. There is insufficient antecedent basis for this limitation in the claim.

6. Claim 41 recites the limitation "column" in line 4. There is insufficient antecedent basis for this limitation in the claim.

7. Claims 62-63 provides use of a mass spectrometer but the claim does not set forth any steps involved in the method/process it is unclear what method the applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

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3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 1, 3, 6, 9-10, 12-16, 18, 20, 23, 25, 27-28, 30-31, 34, 38-39, 41-45, 48-49, 53, 55, 57-59 and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kissmeyer et al. (herein referred "Kissmeyer").

11. Kissmeyer teaches a method and system for determining vitamin D analogs in human and pig serum using liquid chromatography-tandem mass spectrometry. An internal standard is used to spike sample of 1.0 mL of serum. Proteins in the spiked samples precipitate using two volumes of acetonitrile. After centrifugation, the samples are loaded onto a C-18 reversed phase liquid chromatography column. Mass spectrometry is performed on a PE/Sciex API 3000 Mass Spectrometer. The ion source is operated in positive electrospray ionization mode (see abstract and experimental section on pages 118-120). The reference does not disclose performing mass spectrometry on thyroid hormones. It would have been obvious to one having ordinary skill in the art at the time the invention was made to perform a method for conducting mass spectrometry of steroids or vitamin D analogs that will also be performed on another compound such as thyroid hormones, since mass spectrometry is measuring mass ratios and independent of the compound being analyzed.

12. Claims 1,3, 8-10, 12, 14-16, 18, 20, 23, 25, 27-28, 30-31, 36, 38-39, 41, 43-45, 48, 49, 53, 58-59, 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jonsson et al. (herein referred "Jonsson").

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13. Jonsson teaches a method and system for the determination of cortisol in saliva samples using liquid chromatography-electrospray tandem mass spectrometry. Saliva samples are spiked with a deuterium-labeled internal standard. Proteins are precipitated using acetonitrile, then centrifuged. After centrifugation, the supernatant is applied to a C-8 column. Mass spectrometry is performed on an API 3000 LC-MS-MS (see abstract and experimental section pages 64-65). The reference does not disclose performing mass spectrometry on thyroid hormones. It would have been obvious to one having ordinary skill in the art at the time the invention was made to perform the method with a thyroid hormone instead of cortisol as the method in the instant case is for using mass spectrometry to obtain the molecular weights of various fragments.

14. Claims 1, 3-4, 6, 9, 12-16, 18, 20, 23, 24, 27, 28, 30-32, 34, 38, 41-45, 48, 49, 52, 57-59 and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/88548 to Kao et al (herein referred "Kao").

15. The reference Kao teaches a method and system for simultaneously analyzing at least three components of the adrenal pathway using LC-tandem mass spectrometry. The samples can be blood or serum samples and the adrenal pathway components can be progesterone, 17-hydroxyprogesterone, dehydroepiandrostrone, cortisol and 11-deoxycortisol. Samples are spiked with an internal standard, and proteins are then removed from the samples by extraction using methylene chloride. The samples are applied to a C-18 column and the steroid hormones are detected on an API 2000 mass spectrometer, operated in the multiple reaction-monitoring mode (see pages 2,7, 9-10).

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The reference does not disclose performing mass spectrometry on thyroid hormones. It would have been obvious to one having ordinary skill in the art at the time the invention was made to perform the method with thyroid hormones instead of components of the adrenal pathway as the method in the instant case is used for determine molecular weights and independent of what is being analyzed.

16. Claims 1, 3-6, 9, 12, 14-16, 18, 21, 23, 25, 27-28, 30-34, 38, 41, 43-45, 48, 50, 53, 55, 57-59 and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fredline et al (herein referred "Fredline").

17. Fredline teaches a method and system for the determination of aldosterone in samples of plasma or blood. Aliquots of 2 mL are extracted and deproteinated with dichloro-methane/diethyl ether, containing an internal standard. The sample is applied to a liquid chromatography system and analyzed using a tandem mass spectrometer in a selected reaction-monitoring mode. An atmospheric pressure chemical ionization interface is used in a negative ionization mode (see abstract and pages 309-310). The reference does not disclose performing mass spectrometry on thyroid hormones. It would have been obvious to one having ordinary skill in the art at the time the invention was made to perform the method with thyroid hormones instead of aldosterone as the method in the instant case is used for the determine molecular weights and independent of what is being analyzed in plasma or blood.

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18. Claims 1, 3, 7, 12-18, 20, 22, 24, 27-28, 30-31, 35, 38, 41-46, 48-49, 52, 54, 57-59, 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leinonen et al. (herein referred "Leinonen").

19. Leinonen teaches a method and system for analyzing anabolic steroids in using LC-mass spectrometry. The buffered samples are extracted and deproteinated using diethylether. Samples are applied to a C-18 reversed phase chromatography system and investigated using mass spectrometry. Three different modes of ionization are used: electrospray ionization, atmospheric pressure chemical ionization and atmospheric pressure photoionization. All measurements are performed in the positive ion mode. Test samples containing several steroids are investigated (see abstract and pages 694-695). The reference does not disclose performing mass spectrometry on thyroid hormones. It would have been obvious to one having ordinary skill in the art at the time the invention was made to perform the method with thyroid hormones instead anabolic steroids as the method in the instant case is used for determining molecular weights and independent of what is being analyzed.

20. Claims 1, 3, 6, 11-16, 18, 20, 22, 25, 27-28, 30-31, 34, 40-45, 48-49, 52, 55, 57-59 and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vogeser et al. (herein referred "Vogeser").

21. Vogeser teaches a method and system for determining cortisol in serum samples. Serum samples are precipitated with a methanol/zinc sulfate solution containing deuterated cortisol as an internal standard. After vortexing, the samples are

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centrifuged and subjected to HPLC chromatography on a C-18 column. Figure 1 shows a column-switching scheme for an online extraction procedure. Electrospray atmospheric pressure ionization mass spectrometry in the positive mode is used. Multiple reaction monitoring is used (see abstract and pages 944-945). The reference does not disclose performing mass spectrometry on thyroid hormones. It would have been obvious to one having ordinary skill in the art at the time the invention was made to perform the method with thyroid hormones instead of cortisol in serum samples as the method in the instant case is used for determine molecular weights and independent of what is being analyzed.

22. Claims 1-3, 6, 9, 22, 23, 24, 26-27, 28, 29, 30-31, 34, 37-39, 41-45, 47-49, 51, 53, 55, 56-59 and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Brabandere et al (herein referred "De Brabandere"), and further in view of Kissmeyer.

23. De Brabandere discloses a method for the determination of thyroxine in serum. Kissmeyer discloses a method and system for determining vitamin D analogs in human and pig serum using liquid chromatography-tandem mass spectrometry but does not disclose a method for analyzing thyroid hormones. The method of De Brabandere is based on isotope dilution-liquid chromatography /tandem mass spectrometry using electrospray for ionization. An internal standard of $^{13}\text{C}_6$ -thyroxine, approximate 3 mg, was used and HPLC was performed on a C-18 column with an eluent containing methanol/water/formic acid. For electrospray-MS after flow injection of thyroxine two

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different eluent systems were used: water/acetonitrile/ammonia for the detection in the negative ion mode and methanol/water/formic acid for detection in the positive mode. MS measurements were performed in the selected ion monitor and in the selected reaction monitoring mode. In extracting the thyroxine from the serum, approximately 50 ng of thyroxine was pipetted into a conical 5 mL vial where sodium chloride was added and dissolved under vortexing. Then 2 mL of an acetone/30% HCl solution was added and mixed to deproteinize the sample and then subjected to centrifugation. Once the thyroxine was extracted from the serum, a 30 μ L aliquot was injected for LC/MS/MS analysis that was performed on the Hypersil BDS-C-18 column (see abstract, pages 1100-1101, Experimental Section). The De Brabandere reference does not disclose isotope dilution-liquid chromatography /tandem mass spectrometry using steroid samples. The Kissmeyer reference discloses liquid chromatography-tandem mass spectrometry on vitamin D analogs. It would have been obvious to one having ordinary skill in the art at the time the invention was made to perform the mass spectrometry method on thyroid hormones and steroid hormones using different solvents for deproteinizing and washing the column as the method in the instant case is used for determine molecular weights and independent of what is being analyzed and to combine the two mass spectrometry methods to simultaneously analyze two samples.

24. Claims 1-3, 6, 9, 12-20, 22, 25-27, 28, 29, 30-31, 34, 37-39, 41-45, 47-49, 51, 53, 55, 56-59 and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thienpont et al (herein referred "Thienpont"), and further in view of Kissmeyer.

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25. Thienpont discloses a method for the determination of triiodo-L-thyronine in serum using isotope dilution-gas chromatography/mass spectrometry (ID-GC/MS) and isotope dilution-liquid chromatography/tandem mass spectrometry (ID-LC/MS/MS). Kissmeyer discloses a method and system for determining vitamin D analogs in human and pig serum using liquid chromatography-tandem mass spectrometry but does not disclose a method for analyzing thyroid hormones. The Thienpont method discloses an internal standard of $^{13}\text{C}_9$ -thyroxine, approximate 3 ng, was used and the sample pretreatment consisted of deproteinization with pure acetone, extraction, centrifugation and high performance liquid chromatography (HPLC) purification. A conversion of serum thyroxine to T3 was purified by used of a reversed phase C-18 HPLC. For LC/MS/MS a VG Quattro II mass spectrometer was used with a Hypersil BDS-C-18 column with a megaflow electrospray probe and a cross flow counter electrode. In extracting T3 form the serum, 3 mL of serum was pipetted into a conical 5 mL vial followed by the addition of $^{13}\text{C}_9$ -thyroxine. To the vial was added 60 mg of sodium chloride per mL of serum and the mixture was allowed to equilibrate then deproteinated with pure acetone, then subject to centrifugation. After centrifugation the supernatant was purified by HPLC in a C-18 column. Mass spectrometric measurements were performed in the multiple reaction monitoring mode with positive electrospray ionization (see abstract, pages 1924-1928). The Thienpont reference does not disclose performing ID-LC/MS/MS with steroid hormones. It would have been obvious to one having ordinary skill in the art at the time the invention was made to perform the mass spectrometry method on thyroid hormones and steroid hormones as the method in the instant case is used for determine

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molecular weights and independent of what is being analyzed and to combine the two mass spectrometry methods to simultaneously analyze two samples.

26. Claims 60-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of De Brabandere, Thienpont, Kissmeyer, Jonsson, Kao, Fredline, Leinonen or Vogeser.

27. De Brabandere, Thienpont, Kissmeyer, Jonsson, Kao, Fredline, Leinonen and Vogeser do not disclose the aspect where all of the needed/required reagents and instrumentation for analyzing steroid or thyroid hormones in a biological sample into a kit form. It would have been obvious to one having ordinary skill in the art at the time the invention was made to incorporate all of the needed/required reagents and instrumentation required for analyzing steroid and thyroid hormones in accordance with the methods taught by any one of De Brabandere, Thienpont, Kissmeyer, Jonsson, Kao, Fredline, Leinonen or Vogeser in a kit form to make the methods more convenient and easy to perform by having all of the necessary components in one centralized location, facilitating the quick and efficient analysis of steroid and thyroid hormones without having to take extra time to assemble the various reagents and instrumentation required.

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Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine T. Mui whose telephone number is (571) 270-3243. The examiner can normally be reached on Monday-Friday 8-5; Alternate Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Walter Griffin can be reached on (571) 272-1447. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CTM


WALTER D. GRIFFIN
SUPERVISORY PATENT EXAMINER